Health Canada Santé Canada

Canada

Canadian Adverse Reaction Newsletter

Volume 12 • Issue 4 • October 2002

www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/publicat.html

In this Issue

Natural health products: adverse reactions 1
Leflunomide (Arava): hematologic, hepatic and respiratory reactions 2
Case presentation: moxifloxacin 3
Summary of advisories 4
Drugs and grapefruit: interactions 4

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:

www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

Adverse reactions to natural health products

Over 50% of Canadians now use natural health products in the form of traditional herbal products, vitamin and mineral supplements, traditional Chinese, Ayurvedic and other medicines and homeopathic preparations (www.hc-sc.gc.ca/hpb/onhp). There seems to be "an overall misconception that these agents are 'naturally' safe because they come from 'natural' plants."[1,2] The use of herbal products, a type of natural health product, can be associated with adverse effects attributable to factors such as inadequate or excessive dosing, low-quality herbs or supplements, misidentified plant species, variability of constituents, contamination with heavy metals, adulteration with prescription drugs, interactions with prescription drugs and allergic reactions.[1] Also, some herbal ingredients are intrinsically toxic.[2] These factors along with the practice of using health products with multiple ingredients make the evaluation of adverse effects complex.

A number of reported suspected adverse reactions (ARs) to natural health products have been described in this newsletter previously (kava,[3] glucosamine[4,5] and ginkgo biloba[6]). Advisories involving natural health products have also been issued by Health Canada (e.g., aristolochia,[7] ephedra/ephedrine[8] and St. John's wort[9] [www.hc-sc.gc.ca/english/protection/warnings.html]).

With the opportunity for self-selection and the wide availability of natural health products, the public needs to be aware of the possible risks associated with these products as well as their benefits. Many products contain multiple ingredients that may prove challenging for consumers to make informed choices. Furthermore, consumers sometimes receive misleading promotional information about some herbs or ingredients that may either obscure the risks associated with their use or exaggerate their efficacy. Some examples include the presence of ephedra in products used as diet aids or energy boosters, and ginkgo biloba in products promoted as dietary supplements that enhance memory in healthy individuals.

Health care professionals need to know whether their patients are using various health products, including natural health products, certain foods, and prescription and nonprescription drugs, in order to evaluate their overall therapy. Patients may be reluctant to discuss the use of natural health products[1] and may be less likely to report ARs associated with their use than those associated with conventional over-the-counter medicines.[10] Health care professionals should ask their patients if they are using complementary or alternative therapies in order to provide advice and to monitor for possible ARs. As with conventional medicines, specific

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The Marketed Health Products Directorate, in conjunction with the Natural Health Products Directorate and other directorates of Health Canada, continues to monitor the safety of natural health products. All health care professionals and consumers are encouraged to report suspected ARs to these products, and to include the exact product name and list of ingredients if possible, so that more can become known about their safety.

Marielle McMorran, BScPharm,
Health Canada

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2. Barnes J, Anderson LA, Phillipson JD. *Herbal medicines*. 2nd ed. London: Pharmaceutical Press; 2002. p. 1,18-21.
3. Case presentation: Kava. *Can Adverse React Newsl* 2002;12(3):3.
4. Communiqué: Warfarin and glucosamine: interaction. *Can Adverse Drug React Newsl* 2001;11(2):4.
5. Communiqué: Glucosamine sulfate: hyperglycemia. *Can Adverse Drug React Newsl* 2000;10(4):4.
6. Communiqué: Gingko biloba: bleeding disorders. *Can Adverse Drug React Newsl* 2000;10(1):4.
7. *Health Canada advising not to use products labelled to contain Aristolochia* [Public Advisory]. Ottawa: Health Canada; 2001 Aug 17. Available: www.hc-sc.gc.ca/english/protection/warnings/2001/2001_91e.htm (accessed 2002 Aug 16).
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Leflunomide (Arava): hematologic, hepatic and respiratory reactions

Treatment of rheumatoid arthritis has shifted toward earlier and more aggressive therapy with disease-modifying antirheumatic drugs (DMARDs).[1,2] Leflunomide (Arava), a newer immunomodulatory DMARD, is indicated for the treatment of active rheumatoid arthritis in adults.[3]

Because leflunomide has an active metabolite with a long elimination half-life of about 2 weeks, serious ARs (e.g., hepatotoxic, hematotoxic or allergic) may occur even after leflunomide treatment has been stopped.[3] As well, recovery from ARs may be prolonged.[4]

The European Medicines

Table 1: Summary of reports submitted to Health Canada of suspected hematologic, hepatic and respiratory adverse reactions (ARs) associated with leflunomide from Mar. 29, 2000, to May 31, 2002*

System	Reaction term†	Total no. of AR reports†	No. of reports with use of MTX
Hematologic‡	Leucopenia (5); thrombocytopenia (5); anemia (4); granulocytopenia (4); pancytopenia (3); leukocytosis (2); anemia aplastic (1); anemia hemolytic (1); Coomb's direct test positive (1); eosinophilia (1); epistaxis (1); lymphopenia (1); marrow depression (1); prothrombin prolonged (1); purpura (1)	20	8
Hepatic and biliary	Alanine aminotransferase increased (8); aspartate aminotransferase increased (7); hepatic function abnormal (3); phosphatase alkaline increased (2); gamma-glutamyl transferase increased (2); hepatic enzymes increased (1); hepatitis viral (1)	11	1
Respiratory	Dyspnea (5); pulmonary infiltration (4); bronchitis (2); coughing (2); hypoxia (2); pneumonia (1); pneumonia lobar (1); pneumonitis (1); pulmonary fibrosis (1); respiratory disorder (1); respiratory insufficiency (1); upper respiratory tract infection (1)	11	6

Note: MTX = methotrexate.
***These data cannot be used to determine the incidence of ARs because ARs remain underreported and total patient exposure is unknown.**
†Several reaction terms may be listed per AR report; therefore, the same case may be counted under more than one system. Reaction terms are based on the "preferred term" of the World Health Organization (WHO) *Adverse Reaction Dictionary* (WHOART).
‡Includes red blood cell, white blood cell, reticuloendothelial system, platelet, bleeding and clotting disorders.

Evaluation Agency raised concerns about the safety profile of this drug, especially with regard to hepatotoxicity, pancytopenia and serious skin reactions.[5,6] As well, in Canada the manufacturer has issued a safety alert regarding severe and serious hepatic reactions.[7]

From Mar. 29, 2000 (when leflunomide was marketed in Canada) to May 31, 2002, Health Canada received 99 reports of suspected ARs involving the drug, 79 considered to be serious and 4 with a fatal outcome. Three fatal cases were due to respiratory system disorders, with 1 case reporting concomitant use of methotrexate. The fourth fatal case was due to a cardiac system disorder. Suspected hematologic, hepatic and respiratory ARs associated with leflunomide reported to Health Canada are summarized in Table 1. Combined use of leflunomide and methotrexate is associated with an increased risk of toxicity[3] and is not approved in Canada.[7] Nevertheless, a number of the AR reports received described concomitant use.

Concomitant use of leflunomide with DMARDs toxic to liver and bone marrow is not advisable, as such therapy can lead to additive or even synergistic toxicity.[3] Strict vigilance in monitoring liver and bone marrow function is recommended for all patients prescribed leflunomide, particularly if used with other medications associated with increased risk of hepatic or hematologic reactions.[3]

Recommended monitoring parameters are as follows:[3]

- Alanine aminotransferase and aspartate aminotransferase levels before treatment with leflunomide and at monthly or more frequent intervals during the first 6 months, and every 8 weeks thereafter.
- A complete blood count, including differential white blood cell count and platelet count, before treatment with leflunomide and every 2 weeks for the first 6 months, and every 8 weeks thereafter.

It is important to note that, if a severe undesirable effect occurs during treatment with leflunomide, the washout procedures outlined in the product monograph should be followed in order to clear the active metabolite from the body. These washout procedures should also be followed when changing therapy from leflunomide to another DMARD, since the possibility of additive risks of ARs exists for a long time after switching.[3]

Health care professionals are reminded that treatment with leflunomide may have serious hepatic, hematologic and respiratory effects[4] and that these risks may be increased with concomitant methotrexate use.

Lili Loorand-Stiver, BScPhm; Mano Murty, MD, CCFP, FCFP, Health Canada

References

1. Kremer J. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001;134(8):695-706.
2. Schuna A, Megeff C. New drugs for the treatment of rheumatoid arthritis. *Am J Health Syst Pharm* 2000;57:225-37.
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5. *EMEA public statement on leflunomide (Arava): pancytopenia and serious skin reactions* [doc ref EMEA/31637/99]. London (UK): European Agency for the Evaluation of Medicinal Products; 1999 Oct 25. Available: www.emea.eu.int/htms/human/drugalert/drugalert.htm (accessed 2002 Aug 19).
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Case Presentation

Recent cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Please report similar reactions.

Moxifloxacin (Avelox)

Optic neuritis developed in a 22-year-old woman with sinusitis while she was receiving moxifloxacin (Avelox) therapy. After 1 dose she experienced fainting and somnolence, which resolved 2 days after initiation of therapy. After 4 days of treatment she lost vision in her left eye. She consulted an ophthalmologist and continued therapy for 6 days. An MRI scan ruled out multiple sclerosis. The patient was taking birth control pills concomitantly. It was reported that her vision would not likely return.

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

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Summary of health professional and consumer advisories issued since May 24, 2002

Date	Product	Subject and Web address
Aug. 21	Kava	Health Canada issues a stop-sale order for all products containing Kava www.hc-sc.gc.ca/english/protection/warnings/2002/2002_56e.htm
Aug. 13	Aspirin	Health Canada is advising Canadians of incorrect information on new approved uses for Aspirin www.hc-sc.gc.ca/english/protection/warnings/2002/2002_54e.htm
Aug. 8	Aspirin	Important update regarding indications for Aspirin www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/aspirin_asa_e.html
July 30	IV tubing and monitor leads	Notice to hospitals — risk of strangulation of infants by IV tubing and monitor leads www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/iv_tubing_e.html
July 29	Cochlear implants	Notice to hospitals — cochlear implant recipients may be at greater risk for meningitis www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/cochlear_implant_e.html
July	Lioresal	Important safety information regarding Lioresal Intrathecal (baclofen) www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/lioresal_e.html
July 18	Matulane (formerly Natulan)	Important drug safety update for patients using Matulane (procarbazine hydrochloride) capsules (formerly marketed under the name Natulan) — Sigma-Tau Pharmaceuticals, Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/matulane_e.pdf
July 10	Propofol	Notice to hospitals — propofol contraindicated for sedation in pediatric patients receiving intensive care www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/propofol_pediatric2_e.html
July 4	Eprex (epoetin alfa)	Safety update: updated information about Eprex (epoetin alfa) provided to Canadian healthcare professionals — Janssen-Ortho Inc. and Ortho Biotech — consumer information www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/eprex_pa_e.html
June 25	Eprex (epoetin alfa)	Eprex (epoetin alfa) — pure red cell aplasia (PRCA, erythroblastopenia) — Janssen-Ortho Inc. and Ortho Biotech www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/eprex2_e.html
June 21	Drugs and grapefruit juice	Health Canada is advising Canadians not to take certain drugs with grapefruit juice — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_49e.htm
June 19	Seven herbal supplements	Health Canada is warning Canadians not to use seven herbal supplements: Arthrin, Osporo, Poena, Neutralis, Oa Plus, Ra Spes and Hepastat — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_46e.htm
June 14	Bejai Bowyantan	Health Canada is warning Canadians not to use Bejai Bowyantan, a traditional Chinese medicine for infants — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_45e.htm
June 4	Gentamicin sulfate	Important safety reminder for patients using gentamicin sulfate-containing ear drops — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_43e.htm
May 30	Garasone/ Garamycin	Important drug warning: Garasone/Garamycin — Schering Canada Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/garamycin_e.html

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"Its Your Health": The Effects of Grapefruit and Its Juice on Certain Drugs

In an effort to inform consumers of potential interactions between grapefruit juice and certain drugs, Health Canada has issued an "Its Your Health" document on its Web site (www.hc-sc.gc.ca/english/iyh/food/grapefruit.html). The document provides precautions to minimize the risk of adverse effects when consuming grapefruit or its juice, recommendations to consult their health care professional, and additional sources of information. We encourage health care professionals to share this information with their patients.

Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
AL 0201C2
Ottawa ON K1A 1B9
Tel 613 957-0337
Fax 613 957-0335

Health professionals/consumers report toll free:
Tel 866 234-2345
Fax 866 678-6789
Email: cadrmp@hc-sc.gc.ca

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Expert Advisory Committee on Pharmacovigilance, AR Regional Centres and Health Canada staff

Suggestions?
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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Summary of health professional and consumer advisories issued since May 24, 2002

Date	Product	Subject and Web address
Aug. 21	Kava	Health Canada issues a stop-sale order for all products containing Kava www.hc-sc.gc.ca/english/protection/warnings/2002/2002_56e.htm
Aug. 13	Aspirin	Health Canada is advising Canadians of incorrect information on new approved uses for Aspirin www.hc-sc.gc.ca/english/protection/warnings/2002/2002_54e.htm
Aug. 8	Aspirin	Important update regarding indications for Aspirin www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/aspirin_asa_e.html
July 30	IV tubing and monitor leads	Notice to hospitals — risk of strangulation of infants by IV tubing and monitor leads www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/iv_tubing_e.html
July 29	Cochlear implants	Notice to hospitals — cochlear implant recipients may be at greater risk for meningitis www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/cochlear_implant_e.html
July	Lioresal	Important safety information regarding Lioresal Intrathecal (baclofen) www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/lioresal_e.html
July 18	Matulane (formerly Natulan)	Important drug safety update for patients using Matulane (procarbazine hydrochloride) capsules (formerly marketed under the name Natulan) — Sigma-Tau Pharmaceuticals, Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/matulane_e.pdf
July 10	Propofol	Notice to hospitals — propofol contraindicated for sedation in pediatric patients receiving intensive care www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/propofol_pediatric2_e.html
July 4	Eprex (epoetin alfa)	Safety update: updated information about Eprex (epoetin alfa) provided to Canadian healthcare professionals — Janssen-Ortho Inc. and Ortho Biotech — consumer information www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/eprex_pa_e.html
June 25	Eprex (epoetin alfa)	Eprex (epoetin alfa) — pure red cell aplasia (PRCA, erythroblastopenia) — Janssen-Ortho Inc. and Ortho Biotech www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/eprex2_e.html
June 21	Drugs and grapefruit juice	Health Canada is advising Canadians not to take certain drugs with grapefruit juice — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_49e.htm
June 19	Seven herbal supplements	Health Canada is warning Canadians not to use seven herbal supplements: Arthrin, Osporo, Poena, Neutrals, Oa Plus, Ra Spes and Hepastat — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_46e.htm
June 14	Bejai Bowyantan	Health Canada is warning Canadians not to use Bejai Bowyantan, a traditional Chinese medicine for infants — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_45e.htm
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